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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/742,892	12/21/2000	Jack Gauldie	GDI-2	8232

7590 06/27/2003

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/742,892	Gauldie
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 7, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Dec 21, 2000* is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *18*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment, including an amended Sequence Listing and the Declaration of Dr. Vipin Kumar, was received and entered as Paper No. 16 on 4/7/03.

An IDS was received and entered as Paper No. 17 on 4/7/03.

Claims 1-24 are pending, and the elected invention of methods and compositions for treating or preventing a disease caused by *P.acnes* is under consideration.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **Nucleic acid sequences in excess of 10 bases are disclosed at page 19, lines 25 and 29 of the specification, but these sequences are not identified by a SEQ ID NO. Applicant should amend the specification so that all sequences are identified by a SEQ ID NO. For example, page 19, lines 25 and 29 of the specification should be**

amended to identify both sequences by their SEQ ID NOS. It is noted that Applicant provided a new Sequence Listing in Paper No. 16 in which the sequence of SEQ ID NO:1 was amended. However, the sequence at page 19, line 25 that appears to correspond to SEQ ID NO:1 was not amended, so the sequence at page 19, line 25 now has no counterpart in the Sequence Listing. Furthermore, as discussed more fully below, the amendment to the Sequence Listing introduces new matter into the disclosure. If, after determining which sequences are supposed to be in the application, Applicant determines that these sequences are not supported by the instant Sequence Listing, Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

An substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Rejections Withdrawn

The rejection of claim 24 under 35 USC 112, second paragraph for lack of proper antecedent basis is withdrawn in view of Applicant's amendment.

Specification

The amendment filed 4/7/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The deletion of the T residue at position 6 of SEQ ID NO:1, and the addition of SEQ ID NO:3. Applicant has presented no evidence or signed declaration indicating that the presence in the originally filed SEQ ID NO: 1 of the deleted 'T' was an error. In the absence of any justification for this change in the sequence, the change must be considered to be new matter. In order to obtain entry of this amendment Applicant must provide an explanation of how the error occurred, and evidence, such as a signed declaration, that Applicant was in possession of the amended sequence at the time of filing and contemplated its use in the invention.

With regard to the addition to the Sequence Listing of SEQ ID NO:3, Applicant states in Paper No. 16 that SEQ ID NO:3 was in the public domain at the time the invention was filed, citing Miskin (1997). However, the specification as filed does not mention or incorporate by reference Miskin (1997) or any other publication comprising SEQ ID NO:3, and Applicant has

failed to otherwise point to any support in the originally filed specification for SEQ ID NO:3. For these reasons the incorporation of SEQ ID NO:3 into the specification represents new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-24 have been amended to recite "a genetic vaccine utilizing a recombinant vector or modified polypeptides". Although it is not clear what is intended by the term "utilizing" in this context, the claims can be simply interpreted as embracing vaccine compositions comprising a modified polypeptide and a DNA expression vector encoding an antigen. The specification discloses "modified polypeptides" only in the context of the expression products of the "isolated nucleic acids" of the invention (see e.g. paragraph [0016]). While the specification notes that DNA vaccines can be used in conjunction with protein cytokines (see e.g. paragraph [0016]), it discloses "modified polypeptides" only in the context of the expression products of the "isolated

nucleic acids" of the invention, and not in connection with protein cytokines. See paragraph [0038]. Accordingly, it does not provide support for the broader scope of the use of any modified polypeptides of interest together with a DNA vaccine. For example, the specification does not clearly contemplate the use of a composition comprising a DNA vaccine together with a modified polypeptide encoding an antigen or a cytokine. As such, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of filing.

Claims 1-24 have been amended to recite "antigens that do not cause a destructive form of acne". In the interview of 6/18/03, Applicant asserted that support for this limitation could be found in paragraph [0008] of the specification which is reproduced below.

> It is therefore important to identify the type of immune response and the correct target antigen on the pathogen in order to eliminate acne pathology. The inventors have identified and cloned novel antigens of the P. acnes bacterium which can be used to induce protective immune responses. These antigens have not been implicated in the destructive form of acne and in fact, responses against these antigens have not been detected in patients whose unsuccessful immune response to P. acnes was characterized. We believe the molecules we have identified are essential for the organism's growth and colonization of the skin follicle and the eventual inflammatory acne pathology (whiteheads).

This passage indicates that the inventors have cloned P.acnes nucleic acids that encode "novel antigens" that provide a protective immune response, and which "have not been implicated in the destructive form of acne." The meaning of "have not been implicated in the destructive form of acne" is unclear. This phrase could mean that the antigens are not expressed by forms of P.acnes that are responsible for the destructive form of acne. Alternatively it could mean that the antigens themselves are not part of a process that cause destructive acne. In any case, the specification does not explicitly provide support for the limitation, recite "antigens that do not cause a destructive form of acne", and one of skill in the art could not conclude that Applicant

was in possession of this invention at the time of filing. Furthermore, the specification only discloses cloning of a single P.acnes antigen, lipase, and discloses only two other P.acnes antigens by name: hylauronidase and phosphatase. All three of these antigens were known in the prior art (see Miskin (1997) for lipase, and Ingham (1984) for hyaluronidase and phosphatase), and therefore cannot be the "novel antigens" to which the specification refers in paragraph [0008]. For this reason it is unclear to which "novel antigens" the specification refers, and it is not apparent that any novel antigens have been disclosed. As a result, there is not deemed to be adequate support for the new claim limitation that requires that the antigens themselves "do not cause a destructive form of acne" this language represents new matter.

Scope of Enablement

Claims 1-24 stand rejected under 35 U.S.C. 112, first paragraph because the specification fails to enable the full scope of the claimed invention. The specification is enabling for nucleic acid vaccines comprising a P.acnes lipase gene operably linked to a eukaryotic expression control sequence, and for methods of delivering these vaccines to a rodent by intramuscular, subcutaneous, transcutaneous, intraperitoneal, and intravenous administration for the purpose of reducing the size of skin abscesses caused by P.acnes infection. The specification does not reasonably provide enablement for nucleic acid vaccines which do not express P.acnes lipase, the use of nucleic acid vaccines to completely prevent abscesses, routes of nucleic acid vaccine administration other than intramuscular, subcutaneous, transcutaneous, intraperitoneal, and

intravenous, or for methods of treating or preventing acne in any organism other than a rodent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors. Consideration of these factors in the instant case follows.

Nature of the invention and *Breadth of the claims*

The claimed invention under consideration embraces methods and compositions for preventing and treating any disease caused by P.acnes. Claims 1-10 and 19-23 are composition claims that require the following elements:

-a vaccine useful for preventing and treating diseases caused by any pathogen capable of infecting, or avoiding destruction by, macrophages

-a vector comprising at least one nucleotide sequence encoding at least one antigen from the pathogen

-a genetic vaccine utilizing a recombinant vector or a genetic vaccine utilizing modified polypeptides

-antigens that do not cause a destructive form of acne

As discussed below under 35 USC 112, first paragraph, it is unclear whether Applicant intends that the recited "antigens that do not cause a destructive form of acne" must be encoded

by the genetic vaccine, or as a more literal interpretation of the claim would indicate, these antigens must be present in protein form in the vaccine.

In the broadest reasonable interpretation, the elected vaccines must be useful for both completely preventing and treating any disease caused by P.acnes. Claims 11-18 embrace methods of treating or preventing a disease caused by P.acnes in any organism, and embrace a similar scope. Claim 24 is a method of cosmetically improving the appearance of a person suffering from acne vulgaris by administering to the person a vector comprising a nucleotide sequence encoding any P.acnes antigen.

Working examples and guidance in the specification

The specification teaches a single working example of the claimed invention. Mice were vaccinated by intramuscular injection of an adenoviral vector encoding P.acnes lipase, or a control adenoviral vector, and then challenged with P.acnes one week after vaccination. The experimental group showed a decrease in abscess size relative to the control group. No evidence was presented indicating that abscess formation could be totally prevented, and no evidence was presented indicating that vaccination could be used to treat pre-existing acne. The specification teaches no working example with any antigen other than lipase. The specification provides no guidance as to which P.acnes antigens would be expected to provide the greatest protection, nor how to use any of the claimed compositions or methods to completely prevent acne, as required by the claims. The specification provides no working example in any organism other than a mouse.

State of the prior art.

The prior art taught the use of acne compositions comprising P.acnes bacteria and P.acnes bacterial derivatives as acne vaccines. See US Patent 4,057,627 to Stickl, which discloses the use of inactivated P.acnes as an oral vaccine for acne vulgaris. See e.g. claims 1-26, and column 8, lines 35-54. See also the discussion at column 1, line 65 to column 2 line 13 which serves as a short review of the use of P.acnes as a vaccine. A review of the prior art revealed no example of a DNA vaccine against any P.acnes antigen, and no example of complete prevention, i.e. a perpetual cure, of acne by any treatment.

The state of the art of genetic immunization was set forth by McCluskie et al (Molecular Medicine 5(5): 287-300, 1999). McCluskie considers the effects of the routes of administration of DNA vaccines on the quality of any resulting immune response, and considers the relevance of animal models to practice in humans. Pertinent to the instant case, McCluskie teaches that "promising results in animal models have not been realized in human trials and considerable effort is now being focused at understanding this difference and developing ways of improving the efficacy of DNA vaccines." See final sentence of first paragraph on page 288, column 1. McCluskie points out that "[t]he strength and nature of immune responses in mice with DNA vaccines appear to be influenced by a number of factors [citation omitted]; however, these variables may not be of similar importance in larger animals including humans. As such, optimization methods developed in mice may not necessarily be applicable to humans." See page 288, column 2, first full paragraph. In fact, it is clear that some vaccines developed in mice do not

function at all in some primates. At page 296, column 2, second full paragraph, McCluskie states that "[t]he realization that results in mice often do not predict the situation in humans also led to a large number of DNA vaccine studies in non-human primates, including Aotus monkeys, rhesus monkeys, and chimpanzees. IM injection of plasmid DNA vaccines, while highly immunogenic in mice was found to be only relatively so in chimpanzees and essentially not at all in Aotus monkeys. Furthermore, although early human studies have demonstrated the safety and potential of DNA vaccines, results obtained have not been as good as predicted from animal models. Collectively, these results indicate that no animal model may be ideal for prediction of efficacy in humans [citations omitted]." McCluskie concludes that "[it] is difficult to predict from mouse studies the potential of a new vaccine in humans. In fact, in those human trials that have been carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors. Furthermore, although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement to first transfect cells and express antigens, relies on many factors other than immunological responses to the antigen. We will not know the answer to this until after greater experience has been achieved in non-human primates and human clinical trials." Thus the success in primates of vaccines developed in mice is considered by those of skill in the art to be unpredictable.

Regarding the route of administration of the vaccine, McCluskie taught that this variable

"influences the strength and nature of immune responses in mice and non-human primates. However, the results in mice were not always predictive of those in monkeys and this is likely true for humans as well. Optimal dose and immunization schedule will most likely vary between species. It is not clear whether results in non-human primates will be predictive of results in humans, thus additional studies are required." McCluskie tested eight injection-mediated routes including intravenous, intramuscular, subcutaneous, and intraperitoneal, six non-injection routes including the claimed oral, ocular, inhalation, and intrarectal routes, and one transcutaneous route (gene gun). The results indicated that whereas substantial immune responses were obtained by IM, IV, sublingual, and intradermal injection, as well as by gene gun, none of the non-injection routes gave rise to any antibodies. See abstract, and Fig. 1 on page 291. This is objective evidence that the route of DNA delivery influences the immune response obtained in genetic immunization, and that the results obtained by oral, ocular, inhalation, and intrarectal routes are unpredictable.

Regarding the relevance to human disease of the acne mouse model disclosed in the specification, a search of the prior art indicated that the mouse has not been established as an accepted animal model of acne. No citations were discovered in which a mouse was used to study acne lesions such as those described in the instant specification. It is noted that De Young et al (J. Inv. Derm. (83(5): 394-398, 11/1984) developed a rat model for acne by injection of P.acnes into the ear of the animal. However, Whyte et al (J. Comp. Pathol. 122 (2-3): 17-184, 4/2000) taught that while some animal models mimic certain aspects of acne, few represent the

chronic nature of the response seen in the human. Whyte notes that the system of De Young was limited because only histological assessments were made and only a few sites per animal could be tested (page 177, column 2, lines 3-12). Whyte further notes that rodent skin is dissimilar to human skin in terms of its histology, chemical composition, permeability, and arrangement of hair follicles and pilosebaceous glands, and for these reasons the pig is a superior model (page 178, lines 14-19).

Predictability of the invention

In consideration of the scope of the invention embracing phosphatases as antigens, the prior art indicates that P.acnes exocellular phosphatase is not antigenic in mammals. Ingham et al (Br. J. Derm 116(6):805-812, 6/1987) teach that no antibodies to exocellular phosphatase could be detected in humans with acne regardless of the severity of the disease. See abstract. Additionally, Ingham (Br. J. Derm 110(1):61-66, 1/1984) taught that antibodies to P.acnes exocellular phosphatase could not be raised in rabbits. See abstract. Furthermore, each of these references indicates that P.acnes hyaluronidase was substantially less antigenic than lipase. Ingham (1987) teaches that hyaluronidase antibodies were found only in adult humans, and that these adults were far more likely to have lipase antibodies than hyaluronidase antibodies. Ingham (1984) showed that antibodies to hyaluronidase could not be raised in rabbits by injection of the purified antigen, rather *in vitro* incubation of mononuclear cells in antigen was required for induction of an immune response. See abstract. These data demonstrate the unpredictability of raising a preventive, or even protective, immune response to P.acnes exocellular phosphatase and

hyaluronidase specifically, and call into question the predictability of raising protective or preventive immune responses against P.acnes antigens in general.

Regarding the treatment of existing conditions by genetic immunization, Irvine et al (J. Immunol. 156(1): 238-245, 1996) teach that "DNA immunization alone had little or no impact on the growth of established lung metastases", and Lewis et al (Adv. Vir. Res. 54:128-188, 1999) note a case in which genetic immunization resulted in exacerbation of disease progression (see page 169, column 2, lines 1-3 of second paragraph). Furthermore, as noted in the specification and specific to the claimed invention, Karvonen et al (Dermatology 189:344-349, 1994) and Holland et al (Exp. Dermatol. 2:12-16, 1993) teach that immune responses to some P.acnes antigens can actually contribute to the disease process, although neither of these publications, nor Applicant's specification, identifies any of these antigens.

In summary, the state of the art of genetic immunization suggests that it is generally unpredictable which antigens will provide a protective or preventive immune response, the prior art teaches that immune responses to some P.acnes antigens actually contribute to the disease process but fails to identify antigens that do this, and some P.acnes antigens are poorly or undetectably antigenic in mammals. Also, the significance of results in the disclosed animal model are unknown because it is not an art recognized animal model of human acne, and because the prior art teaches that genetic immunization of mice may not be predictive of results in primates. The specification fails to teach which P.acnes antigens, other than lipase, will provide a protective immune response, and fails to teach how to use any P.acnes antigen to totally prevent any disease

associated with P.acnes. The specification fails to provide any technical guidance that would improve the state of the art of genetic immunization in general, and therefore does not reduce the unpredictability associated with genetic immunization in general, or with P.acnes immunization specifically. Given the state of the art, the unpredictability of the art, the level of exemplification, and the teachings in the specification, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Written Description

Claims 1-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As discussed above, the claimed invention is drawn to nucleic acid vaccines encoding any P.acnes vaccine that can be used to treat or prevent a disease caused by P.acnes. Claims 1-9 and 11-24 embrace any P.acnes antigen that can cause an immune response in a recipient. Claim 10 is limited to the genus of antigens encoded by any P.acnes lipase, hyaluronidase, or phosphatase gene.

The following analysis is based on the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage on the treatment of genus claims is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The specification teaches how to isolate lipase genes by PCR but fails to identify by complete structure any nucleic acid encoding any antigenic P.acnes polypeptide. The specification discloses no relevant structural characteristics such as correlation between nucleic acid or polypeptide structure and the antigenic function required by the claims. The scope of even the narrowest claim, claim 10, embraces numerous naturally occurring structural variants, including allelic variants. The claimed genus is highly variant because the only structural requirement is the encoded proteins must be antigenic in a host. However, as noted above under enablement, it is not clear which P.acnes proteins are antigenic and which are not, and the specification provides no guidance in this matter. The specification teaches no structural features that could distinguish the compounds of the claimed genus from other antigenic proteins, and no common structural attributes identify the members of the claimed genus.

The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic

acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., antigenicity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for the genus of antigenic polypeptides and polypeptide fragments. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). As there is no disclosure of the polynucleotides, the

skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The failure to disclose any member of the genus by complete structure, or to disclose appropriate identifying characteristics of the species of the claimed genus, combined with the breadth and the variability of the claimed nucleic acids, results in a finding that one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of filing.

Additionally, the claims have been amended to recite "a genetic vaccine utilizing a recombinant vector or modified polypeptides, the vaccine further comprising antigens that do not cause a destructive from of acne." This amendment raise two new grounds of rejection for lack of adequate written description.

First the scope of "modified polypeptides" must be considered. In view of the specification at paragraphs [0038], [00390, [0041], [0044] and [0046], these modified polypeptides are considered to be antigens that are active components of the vaccine, i.e. they can be used to treat or prevent acne as part of a vaccine. Therefore the claimed genus embraces the

set of modified polypeptides that can be used to treat or prevent acne. Paragraph [0038] defines "modified polypeptides" as including "subfragments, deletion mutants, processing mutants, or substitution mutants, polypeptides having the same secondary structure as the binding region of the native polypeptide, and combinations thereof." By "binding region" it is assumed that Applicant intends epitope. The specification fails to describe any epitope that can be used to treat or prevent acne. Further the specification fails to describe what mutants of the antigens or their binding regions can be used treat or prevent acne. Put another way, Applicant is claiming a physical product, a vaccine, the function of which is utterly dependent on its structure, but the claims and specification recite only functional limitations, and not structural limitations.

In order to adequately describe the claimed invention, the specification must adequately describe a representative number of species. This can be done by reduction to practice or by description of relevant identifying characteristics, such as a description of functional characteristics coupled with a known or disclosed correlation between structure and function. The specification reduces to practice a single species of the claimed invention, but fails to provide any correlation between structure and function that would suffice as a description of any "modified polypeptide" that can be used to treat or prevent acne.

Second, the genus of "antigens that do not cause a destructive form of acne" must be considered. Applicant asserts at paragraph [0008] that

> The inventors have identified and cloned novel antigens of the P. acnes bacterium which can be used to induce protective immune responses. These antigens have not been implicated in the destructive form of acne and in fact, responses against these antigens have not been detected in patients whose unsuccessful immune response to P. acnes was characterized. We believe the molecules we have

> identified are essential for the organism's growth and colonization of the skin follicle and the eventual inflammatory acne pathology (whiteheads).

However, the specification only discloses cloning of a single P.acnes antigen, lipase, and discloses only two other P.acnes antigens by name: hylauronidase and phosphatase. All three of these antigens were known in the prior art and therefore cannot be the "novel antigens" to which the specification refers in paragraph [0008]. As such the specification fails to provide any structural description of any novel antigen that causes a destructive from of acne. For this reason it is unclear to which "novel antigens" the specification refers, and it is not apparent that any novel antigens have been disclosed. Even if Applicant did intend to refer to the disclosed lipase, hyaluronidase, and phosphatase genes as antigens that do not cause a destructive form of acne, the specification fails to provide any description of any unifying structural or functional characteristic that these antigens have in common such that one of skill in the art could immediately envisage which of the other P.acnes antigens were also members of the genus. Thus the specification fails to describe a representative number of species by any identifying characteristic other than function. As discussed above, it is not sufficient to define a polynucleotide solely by its principal biological property, e.g. useful for treating and preventing a disease caused by P.acnes, because disclosure of no more than that is simply a wish to know the identity of any polynucleotide with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it

from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the polynucleotide has been isolated. Thus, claiming all polynucleotides that achieve a result (e.g. treatment and prevention of a disease caused by P.acnes) without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Accordingly, one of skill in the art could not conclude that Applicant was in possession of either the genus of "modified polypeptides" that can be used to treat or prevent acne, or the genus of antigens that do not cause a destructive form of acne, at the time the invention was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are also indefinite because it is unclear what is intended by "a genetic vaccine utilizing... "modified polypeptides". Specifically, it is unclear if the claims are intended to embrace genetic vaccines comprising modified polypeptides, or alternatively genetic vaccines

encoding modified polypeptides, or whether both of these possibilities are intended to be embraced. For the purpose of examination, this language has been interpreted as meaning "comprising modified polypeptides", rather than "encoding modified polypeptides". This interpretation is supported by the specification at paragraphs [0041] and [0046] which state:

> "Those skilled in the art will appreciate that the vectors, polynucleotides **and/or** polypeptides of the subject invention can be administered by a number of widely recognized and known methods of administration."

And

> "Alternatively, the subject vectors, polynucleotides **and/or** polypeptides are administered using liposomal technology."

Emphasis added.

Claims 1-24 are indefinite because it is unclear what is the intended scope of "a destructive form of acne". This phrase is not defined in the specification, the specification sets no standard against which to compare, and sets forth no indicia of destruction, thus one of skill in the art cannot know the metes and bounds of the claims. Also, and it not clear that there is any form of acne that is not destructive to some extent, so it is unclear what material Applicant intends to exclude from the invention.

Response to Arguments

Applicant's arguments, and the Declaration of Dr. Kumar, filed 4/7/03 have been fully considered but they are not persuasive.

At the paragraph bridging pages 5 and 6 of the response Applicant addresses the issue of the animal model as it reflects on the enablement of the claimed invention. Applicant cites Archer v. Papa, Engelhardt v. Judd, Scott-Bruton v. Finney, and SmithKline v. Apotex to support the notion that successful use of a compound on laboratory animals may be sufficient proof of utility to establish actual reduction to practice. These decisions do not provide sufficient basis to require withdrawal of the rejection because the evaluation of the correlation between results obtained in an animal model and the results that might be obtained in a human must be made on the totality of the available evidence of record. See MPEP 2164.02. In this case the Office has provided evidence that the animal model disclosed in the specification is not an art-accepted animal model, that there are physiological differences between mice and humans that render extrapolations of acne treatments unpredictable, that generally speaking, the extrapolation of genetic immunization results in mice to those that might be obtained in humans is unpredictable. In fact, the passage quoted from SmithKline v. Apotek at page 6 of the response supports the position of the Office inasmuch as it acknowledges that positive results in animal models indicate "only a possibility of like chemical behavior" in humans. In this case, the possibility of "like chemical behavior" is deemed to be very low due to the art-recognized physiological differences between human and rodent skin, e.g. in terms of its histology, chemical composition, permeability, and arrangement of hair follicles and pilosebaceous glands, the fact that mice do not naturally suffer from acne, and the unpredictability in extrapolating genetic immunization results from mice to humans.

Applicant appears to rely on *In re Krimmel* to support the position that the invention need not be practiced on humans, but could be patentable for use on animals. This argument is unpersuasive because Applicant has not shown that acne exists in any organism besides a human, and because claim 24 explicitly requires that the invention must work in a human, specifically a "person".

In the Declaration, Dr. Kumar states the opinion that each of the 24 claims is enabled, and relies for support on several references. The relevance of the evidence in these references is considered below.

Throughout the Declaration Dr. Kumar notes that there have been at least 509 gene therapy clinical trials since the 1980's. This in itself is not considered to be evidence of enablement because Dr. Kumar does not point to a single example of success in any of these clinical trials, and because it is not apparent that any of these trials were aimed at genetic vaccines for acne. None of the other 25 cited references provides evidence to overcome the position of the Office regarding the relevance of the animal model of acne, or provides any evidence that an art accepted rodent model of acne exists. None of the cited references provides evidence that the extrapolation of mouse genetic immunization results to humans is routine and predictable, particularly with respect to immunization against P.acnes. Thus, the opinion of Dr. Kumar that the claimed invention is enabled is unpersuasive because it is not supported by evidence that is pertinent to the grounds of the rejection.

While the Tacket and Graham references provide examples of recombinant vectors that generate immune responses, neither these references, nor the existence of GlaxoSmithKline's ENGERIX-B, provide evidence pertinent to the mouse model of acne, or the general predictability of extrapolating mouse results to humans, particularly in the case of acne.

The Tebbutt, Cotter, and Broder references deal with vectors available for gene therapy applications, but the Tebbutt and Cotter References do not even mention genetic vaccines, and none of the references deals with the specifics of the enablement rejection.

It is noted the Gabaglia (1999), Stewart (1999), and Pamer (1998) references deal with cell-mediated immunity and the ability to facilitate cell-mediated, rather than humoral responses. Additionally the Putzer and Diehl references are relied upon to support the use in genetic vaccines of nucleic acids encoding costimulatory molecules for stimulating effective T-cell responses. This is pertinent in view of the teachings in the prior art regarding the fact that P.acnes hyaluronidase and phosphatase tend not to stimulate humoral immunity, and that these antigens could be presented on the surface of antigen presenting cells due to the fact that P.acnes invades macrophages. The implied argument is that the claimed compositions and methods could work through a cell-mediated mechanism, rather than one that depends on a humoral response, so the failure to stimulate humoral immunity may not be indicative of a lack of enablement. This is unpersuasive because many antigens stimulate cell-mediated immune responses in rodents, including the antigen studied by McCluskie (1999) (see e.g. paragraphs bridging columns 1 and 2 on pages 292 and 293), yet those of skill in the art still consider the extrapolation of genetic

immunization results from mice to humans to be unjustified in view of the totality of the art. Furthermore, no evidence was presented that any P.acnes antigen elicits a cell-mediated response in a human that would enable prevention of treatment of acne.

The Miskin (1997), Hynes (2000), and Ostanin (1992) references concern only the procurement of P.acnes lipase, hyaluronidase and acid phosphatase genes. While it is not articulated in the Declaration, this may have been intended as evidence of adequate written description. However, Applicant is reminded that *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, makes clear that the written description provision of 35 U.S.C 112 is severable from its enablement provision (see page 1115). So, an argument that one is enabled for the isolation of particular genes from an organisms is not evidence that one has in their possession of the recited molecules at the time of the invention, and would not overcome the written description rejection. These references are not persuasive of the enablement of the invention because they present no evidence pertinent to the mouse model of acne, or the general predictability of extrapolating mouse results to humans, particularly in the case of acne.

The Karvonen, Holland, and Ingham references were discussed in the enablement rejection, These references present no evidence pertinent to the mouse model of acne, or the general predictability of extrapolating mouse results to humans, particularly in the case of acne.

The Gribbon (1993), Kearney (1984), Higaki (1996), and Hynes (2000) references are cited in support of an embodiment of the invention in which the genetic vaccine produces antibodies that are inhibitory to the function of P.acnes lipase, hyaluronidase, or acid phosphatase

proteins, thereby inhibiting cell growth. These references provide no evidence that inhibitory antibodies against these enzymes have been, or can be, produced. Furthermore, the evidence of record indicates that P.acnes hyaluronidase and acid phosphatase are poorly antigenic, such that it is entirely unpredictable as to whether or not inhibitory antibodies could be obtained in a human. Additionally, they present no evidence pertinent to the mouse model of acne, or the general predictability of extrapolating mouse results to humans, particularly in the case of acne.

The Gerdts (2000), Babiuk (2000), Xiang (199), Glenn (2000), and Lewis (1999) references are relied upon to support various routes of administration. Dr. Kumar declares at paragraph 18 that ocular, rectal, and intrathecal routes, as recited in claim 12, were not used at the time of filing. In view of the unpredictability of the art in general, as established above, one of skill in the art would have no reason to expect to obtain successful treatment of acne using these routes of administration. With regard to the remaining routes of administration, the same concerns apply regarding the relevance of the mouse model of acne, and the general predictability of extrapolating mouse results to humans, particularly in the case of acne.

Applicant has not explicitly responded to the written description rejection.

For these reasons the Applicant's arguments, and the Declaration of Dr. Kumar are unpersuasive and the rejections are maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7, 10-12, 15, 16, 20, 21, 22, and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Stickl (US Patent 4,057,627, 11/8/1977), as evidenced by Taverne et al (Infection and Immunity 37(3):927-934 (9/1982)).

Stickl teaches compositions comprising attenuated P.acnes and their use as oral vaccines for acne vulgaris. See e.g. column 4, lines 12-16; column 8, lines 35-54; and claims 1-26. Note that Stickl refers to "Corynebacterium acnes", rather than P.acnes. The designation "Corynebacterium acnes" was changed to P.acnes after the publication of Stickl, so one of skill in the art appreciates that Corynebacterium acnes and P.acnes are the same organism. See e.g. Taverne et al (Infection and Immunity 37(3):927-934 (9/1982), abstract). The Stickl disclosure anticipates instant the claims because inactivated P.acnes is considered to be a vector comprising nucleic acids encoding all P.acnes antigens. Because the nucleic acid encodes all P.acnes antigens, the vaccine can be considered to comprise nucleic acids encoding antigens that do not cause a destructive form of acne, as well as an adjuvant as required by claims 7 and 22. Stickl also teaches that the vaccine may be disposed within a bottle as required by instant claim 20. See column 6, lines 44-52. The vaccine may be aqueous as required by instant claim 21. See abstract. Absent evidence to the contrary, the vaccine of Stickl is considered to contain a variety of

modified polypeptides such as phosphorylated polypeptides, prenylated polypeptides, and polypeptides containing prosthetic groups such as e.g. thiamine pyrophosphate.

Response to Remarks

Applicant's arguments filed 4/7/03 have been fully considered but they are not persuasive. Applicant asserts that none of the references cited anticipate the claims as amended. This is unpersuasive because it is a statement of opinion and is unsupported by any argument or evidence. Stickl teaches a vaccine comprising attenuated P.acnes. Applicant might argue that his does not constitute a "genetic vaccine", however a search of the prior art indicates that "genetic vaccine" is a term of art that applies to attenuated bacterial vaccines. See e.g. Merz (JAMA (1987) 258(15): 2028). An argument that the genetic vaccine of Stickl does not comprise a recombinant vector would be unpersuasive because the claims do not require that the vaccine must be recombinant. As claimed, the vaccine may utilize a recombinant vector or, *in the alternative*, modified polypeptides. The vaccine of Stickl comprises modified polypeptides, as discussed above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 1, 2, 4-15, and 17-23 which are drawn in part to non-elected inventions. Applicant did not traverse the restriction requirement. A complete reply to the final rejection must include cancellation of non-elected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to

the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.